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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,552	LEVITEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2005 and 21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,17,18 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,17,18 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-22-05 has been entered.

The amendment filed 11-22-05 has not been entered because it was non-compliant. The amendment filed 2-21-06 has been entered.

Applicant's arguments filed 11-22-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7, 9-16 and 19-25 have been canceled. Claims 26-30 have been added. Claims 8, 17, 18 and 26-30 are pending and under consideration in the instant office action.

The Declaration by Michael Leviten filed 11-22-05 attempting to swear behind Stanley (April 2000) is moot because of the effective filing date of the claims as newly amended and because the 102 (a) rejection over Stanley has been withdrawn.

Specification

The amendment filed 3-28-05 remains objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The addition of the application numbers added to the paragraph starting on pg 10, line 5, remains new matter. No support for the patent applications is found in the specification as originally filed. The scope of the new applications is different than that of those originally contemplated. Accordingly, the new patent application numbers are new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 101

Claims 8, 17 and 18 remain rejected and claims 26-30 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record.

Claims 8, 17, 18 and 26-30 are directed toward a transgenic mouse whose genome comprises a disruption in the Cerberus (Cer1) gene, said disruption comprising replacement of nucleotides corresponding to bases 241-528 of SEQ ID NO: 1 with a Neo cassette.

The specification teaches making Cer1 -/- mice (pg 51, lines 1-6). Two homozygous mice were tested in an open field test (pg 51, lines 9-14; pg 52, Table 1). Applicants conclude that increased number of fecal boli during the ten-minute test indicated the mice had increase anxiety.

The mice claimed and described in the open field test study do not have a specific or substantial utility. It is not readily apparent that the results are statistically significant because only two knockout mice were tested. The results of the open field test merely indicate the mice defecated more frequently. It cannot be concluded that increased defecation is a sign of anxiety and not some muscular or gastrointestinal dysfunction. Significant "further experimentation" would be required to use the results of the open field test to determine the function of the cerberus gene. As such, mice with a disruption in the cerberus gene comprising SEQ ID NO: 1 that defecate more frequently than a wild-type mouse in an open field test does not have utility as a model for anxiety.

The specification suggests using the mice as a model of disease, specifically as a model for neurological phenotypes (pg 17, line 30). The mice claimed do not have utility as a model of disease. The specification does not correlate any disease in humans to increased anxiety as claimed. The specification does not correlate increased anxiety found in humans to a disruption in a cerberus gene. Therefore, using the mice as a model of disease is not a specific or substantial utility.

The specification suggests using the mice to identify agents that ameliorate a phenotype (pg 18, line 8). Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility" because the mouse may not be capable of identifying agents capable of treating disease. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught,

> "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, line 4 on).

Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or GPCR-like protein in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not the cerberus protein itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice. Furthermore, the specification does not identify any such agents using the mice. Therefore, using the mice to identify agents that alter the increased sensitivity to pain is not a specific, substantial or credible utility.

The specification suggests using the mice to identify agents that affect cerberus function (pg 18, lines 30-31). The mouse claimed couldn't be used to identify agents that act on cerberus because the mice do not express cerberus.

It was "well-known" in the scientific community at the time of filing to knock out a gene in a mouse in an attempt to determine its function; however, it was also "well-known" that the mouse may only provide clues to the function of the gene and that the mouse may not be capable of determining the function of the gene. While the mouse may have "scientific utility," "scientific utility" is not the same as "patentable utility" or a "well-established" utility.

The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention as a model of disease. Further study would be required to determine the function of the disrupted gene. The overall phenotype of the applicants' mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to

study a disorder. Thus, using the mice claimed for further research is not a "substantial utility."

Using the mice to identify the function of the knocked out gene is not a "substantial utility" or "specific utility" because the phenotype may be caused by other proteins compensating for the deleted gene. Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype may be a result of other compensating proteins and not the knocked out gene.

The function of a gene may not be found by studying a knockout mouse. Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) used knockout mice that had increased anxiety further study to determine the function of $GABA_B$ receptor. Mombereau did not teach how to use mice with decreased anxiety as

claimed. In addition, Mombereau did not determine the function of the $GABA_B$ receptor. Mombereau administered compounds known to antagonize $GABA_B$ receptor (found in *in vitro* assays, not in the mice) to the mice. Mombereau concluded that the mice merely confirmed $GABA_B$ was involved in a molecular pathway relevant for the manifestation of anxiety or depression. Mombereau did not determine the function of $GABA_B$ receptor using the $GABA_B$ -/- mice. Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). Therefore, using a mouse to merely obtain clues of the role of a protein in a molecular pathway of anxiety or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of the protein within the pathway.

The disruption is not specific to the Cerberus gene because other genes may be affected by the targeting construct. Scarff (genesis, 2003, Vol. 36, pg 149-157) taught the phenotype of knockout mice may be a result of the retention of the selectable marker gene in the mice, which affects expression of neighboring genes, i.e. the observed phenotype may not be a result of the disruption of the gene itself.

> It is becoming apparent that retention of the selectable marker gene in knockout mice can lead to a confounding phenotype. In most cases the retained selectable marker gene affects the expression of neighbouring genes."
> (pg 155, col. 1, 2nd full ¶).

Scarff cites Fiering (Gene Dev., 1995, Vol. 9, pg 2203-2213); Hug (Mol. Cell Biol. 1996, Vol. 16, pg 2906-2912); Pham (PNAS, 1996, Vol. 93, pg 13090-13095); Leder (Blood, 1997, Vol. 90, pg 1275-1282); DeJarnette (PNAS, 1998, Vol. 95, pg 14909-14914; and Ren (Dev. Dyn., 2002, Vol. 225, pg 305-315). Without evidence to the contrary, any abnormal phenotype observed in the mice described by applicants is not specific to the disruption in the gene itself because it may be a result of the selectable marker gene affecting neighboring genes. Therefore, the mice claimed do not have a utility that is specific to the Cerberus gene disruption.

Overall, the mice claimed do not have a "well-established utility" because applicants have not taught how to learn more about the Cer1 using mice that defecate more than normal, have decreased velocity or distance traveled in an open field test or hang longer in a tail suspension test. The mice claimed do not have a substantial utility because applicants have not provided any blaze marks for those of skill to use the mice claimed in any further research. Applicants have not linked increased defecation with fear, anxiety or hypoactivity with

statistical significance because increased defecation could be caused by a muscular or gastrointestinal dysfunction and not anxiety or fear or linked velocity or distance traveled in an open field test to hypoactivity. Accordingly, applicants have not substantially linked the Cer1 gene disruption to anxiety, fear or hypoactivity.

Applicants argue that one of skill would have recognized that the mouse has a well-established utility for defining the function and role of the disrupted gene, i.e. a tool in studying gene function (pg 6 of response filed 11-22-05). MPEP 2701 II(A)(3) states:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. (underlining added for emphasis)

Applicants' arguments are not persuasive. Applicants used the mice in phenotype analysis tests, but applicants have not determined the function of the gene. Applicants noted that the mice defecated more than normal, had decreased velocity and distance traveled in an open field test and hung longer immobile in a tail suspension test; however, no correlation between increased defecation and increased anxiety exists because the observed increased defecation may have been caused by a muscular or gastrointestinal disorder. Decreased velocity and distance traveled and increased time immobile may be a neuromuscular problem and not an indication of "hypoactivity." In fact, only two mice that defecated more than normal is not statistically significant

because the n number is too small and because the increase is not statistically different than normal. Accordingly, scientists cannot concluded that the observed increased in fecal boli was caused by the disruption in the Cer1 gene. Using the mice for "further research" of the cerberus gene is not a specific or substantial utility because applicants do not provide any blaze marks to perform such "further research." The specification does not teach those of skill know how to use mice that defecate more frequently than normal to research the Cer1 gene. The MPEP states a well-established utility must be specific, substantial and credible. In this case, using the mice to determine the function of the cerberus gene rises merely to the level of a scientific utility, but does not rise to the level of a specific, substantial and credible utility. One of skill would not gain any additional information of the role of the Cerberus gene by repeating the open field test and observing the mice walk slow and defecate. The mice claimed do not compare to "gas chromatographs, screening assays and nucleotide sequencing techniques" because applicants do not teach how to use the mice to gain any additional information about the Cer1 gene.

Applicants argue at least three pharmaceutical companies subscribe to the DeltaBase and one pharmaceutical company has ordered the claimed mouse; therefore, applicants conclude that those of skill would recognize the utility of the mice (pg 7). Applicants' argument is not persuasive. Sales may be evidence to overcome a 103 obviousness rejection, but there is no case law that establishes that "sales" are evidence of patentable utility. Evidence of sales is not evidence the mice have a "well-established" utility or a "specific utility" or a "credible utility." In fact, the one

pharmaceutical company that bought the mice may have been the ones who determined how to use the mice in substantial research. The instant application does not teach how to use the mice claimed for any further substantial research. The DeltaBase is not relevant to the claimed subject matter because the data in the DeltaBase does not teach how to use the mice claimed in any further substantial research.

Applicants argue the mice can be used to study the function of Cer1 within the realms of fear, anxiety and hypoactivity. Applicants' argument is not persuasive. Increased fecal boli is not statistically significant in the population of knockout mice and cannot be linked to the Cer1 disruption. Increased fecal boli is also not linked to fear, anxiety or hypoactivity. Therefore, the Cer1 disruption cannot be linked anxiety, fear or hypoactivity. More importantly, the specification does not teach how to study the function of Cer1 within the realm of fear, anxiety and hypoactivity using mice that defecate more than normal.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure (pg 10). Applicants argue that contrary to the product in En re Brenner, whose sole 'utility' consisted of its potential role as an object of use-testing, the mouse claimed can be used to determine the function of SEQ ID NO: 1. Applicants' arguments are not persuasive. *In re Schoenwald*, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. The examiner has challenged all of the asserted utilities in the disclosure and has

challenged what applicants consider "well-established" utilities. The mouse claimed might only provide a clue to a pathway in which SEQ ID NO: 1 is involved. This is not a specific utility because results from the tests only indicate SEQ ID NO: 1 is involved in a pathway relating to anxiety. Assuming the phenotype observed is statistically significant and can be linked to the Cer1 gene disruption, the phenotype at best provides only a clue that SEQ ID NO: 1 is generically involved in a pathway having a number of proteins. Using the mouse to determine the function of SEQ ID NO: 1 is not credible or substantial because the function of SEQ ID NO: 1 may never be found using the mouse. Assuming further study of the mouse will elucidate the function of SEQ ID NO: 1, the amount of research required to do so would be significant. The specification does not guide those of skill in any particular direction so that one of skill could simply perform an assay to determine the function of SEQ ID NO: 1.

Applicants' argument regarding Crawley is noted but does not address whether the increased defecation observed in an open field test is statistically significant or how increased defecation is linked to anxiety or fear.

Applicants argue Olsen fails to support the examiners position that the knockout mice claimed do not have a substantial use in studying Cer1 gene function. Applicants' argument is not persuasive. Olsen did not reveal the function of the GABA gene using the knockout mice. In this case, applicants have not taught how to learn more about the Cer1 using mice that defecate more than normal. The mice claimed do not have a substantial utility because

applicants have not provided any blaze marks for those of skill to use the mice claimed in any further research. Furthermore, applicants have not linked the Cer1 disruption with increased defecation with statistical significance because the n number used was too small, because the increased defecation observed was not statistically increased as compared to normal mice. Applicants have not linked increased defecation with fear, anxiety or hypoactivity with statistical significance because increased defecation could be caused by a muscular or gastrointestinal dysfunction and not anxiety or fear. Accordingly, applicants have not substantially linked the Cer1 gene disruption to anxiety, fear or hypoactivity.

Applicants argue Austin and the NIH report should be considered because the "references are not being cited to support a post-filing assertion of utility." Applicants state the "goal of determining gene function is clearly set forth in the specification" (pg 12). Applicants' arguments are not persuasive. Applicants have not taught how to learn more about the Cer1 using mice that defecate more than normal. Nor have applicants linked the Cer1 disruption with increased defecation with statistical significance because the n number used was too small, because the increased defecation observed was not statistically increased as compared to normal mice. Nor have applicants linked increased defecation with fear, anxiety or hypoactivity with statistical significance because increased defecation could be caused by a muscular or gastrointestinal dysfunction and not anxiety or fear. Accordingly, applicants have not

substantially linked the Cer1 gene disruption to anxiety, fear or hypoactivity. Austin and the NIH report do not discuss how to use mice with a disruption in the Cer1 gene.

Applicants argue the examiner's position that the observed phenotype may not be a result of the Cer1 disruption is based on conjecture. Applicants argue the examiner has not show the observed phenotype IS a result of the targeting construct affecting other genes. Applicants conclude those of skill in the art would accept the observed phenotype is associated with the Cer1 gene. Applicants' conclusion is erroneous. Scarff clearly provides evidence that those of skill would question whether an observed phenotype was actually caused by the disruption of the desired gene. The examiner must weigh the fact that the observed phenotype may not be a result of the Cer1 disruption in determining whether the mice claimed have utility. Especially in view of the fact that only two mice defecated more frequently than other mice, which is not statistically significant. Applicants have substantially linked the phenotype to the Cer1 gene disruption.

Claim Rejections - 35 USC § 112

Enablement

Claims 8, 10, 17 and 18 remain rejected and claims 26-30 are rejected under 35 U.S.C. 112, first paragraph for reasons of record. The claimed invention is not supported by either a specific or substantial asserted utility or a well established utility

for the reasons set forth above; therefore, one skilled in the art clearly would not know how to use mice having a disruption in SEQ ID NO: 1 as claimed.

Applicants' arguments to the enablement rejection are found in the arguments to the utility rejection, which have been addressed above in the utility rejection.

New Matter

Claims 8, 17 and 18 remain rejected and claims 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "corresponding to bases 241-528" in claim 8 is new matter. The breadth of "corresponding to" is greater than replacing bases 241-528 as originally described.

The phrase "anti-depressive" behavior in claim 17 is new matter. Support cannot be found in the specification as originally filed.

Indefiniteness

Claims 8, 17 and 18 remain rejected and claims 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of a "cerberus gene" in claim 8 as newly amended are

indefinite. The specification defines a gene as "(a) a gene containing at least one of the DNA sequences disclosed herein; (b) any DNA sequence that encodes the amino acid sequence encoded by the DNA sequences disclosed herein and/or; (c) any DNA sequence that hybridizes to the complement of the coding sequences disclosed herein" (pg 4, lines 26-30). The specification specifically states "cerberus gene" refers to a sequence comprising SEQ ID NO: 1 or comprising the sequence identified in GenBank as Accession No.: NM_009887; G1: 6753409. In one aspect, the coding sequence of the cerberus gene comprises SEQ ID NO: 7 or comprises the gene identified in Genebank as Accession No. NM_009887; G1:6753409 and encodes for a Cer1 polypeptide" (pg 6, lines 21-25). However, SEQ ID NO: 1 and 7 are mouse cerberus cDNA and cannot be considered a "cerberus gene" as stated in applicants' definition. Numerous other genes share structural and functional homology with Cer1 and would hybridize to the complement of SEQ ID NO: 1 or 7. In addition, any gene would "hybridize to the complement of the coding sequences disclosed herein" to some degree. Therefore, the metes and bounds of what applicants consider a "cerberus gene" are unclear.

Claim 8 as newly amended is indefinite because the metes and bounds of nucleotides that "correspond to bases 241-528 of SEQ ID NO: 1" cannot be determined. It is unclear if the phrase refers to bases having the same position, function, nucleic acid sequence or components. For example it is unclear if the phrase encompasses bases that also encode a particular domain type or bases that are in the same position in homologs of the cerberus gene or any segment of a cDNA that is also made up of

nucleotides.

The metes and bounds of Claim 17 remains rejected for reasons of record regarding the phrase "anti-depressive" which has been re-introduced into the claim.

Claim 26 is indefinite because one mouse cannot have a decreased "average" velocity. While the velocity of the mouse may be decreased as compared to the average of wild-type mice, the "average velocity" of the mouse is not decreased as claimed. If the "average velocity" of the mouse is somehow calculated during the open field test, please clarify.

Claim 27 is indefinite because it is unclear how the limitation further limits claim 26, i.e. does the mouse have decreased average velocity, decreased total distance traveled AND hypoactivity or does the decreased average velocity and decreased total distance traveled indicate the mouse is hypoactive.

Likewise, claim 30 is indefinite because it is unclear how the limitation further limits claim 29, i.e. does the mouse have increased number of fecal boli AND fear, anxiety or nervousness or does the increased number of fecal boli indicate the mouse has fear, anxiety or nervousness.

Claim Rejections - 35 USC § 102

The rejection of claims 8, 17 and 18 under 35 U.S.C. 102(a) as being anticipated by Stanley (Genesis, 2000, 26: 259-264) has been withdrawn because Stanley did not replace nucleotides of the cerberus gene with a Neo cassette as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 17, 18 and 26-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Belo (Genesis, April 2000, Vol. 26, pg 265-270).

The effective filing date of the claimed invention is 6-21-01, the filing date of the instant application, because provisional applications 60/213670, 60/266046 and 60/282668 did not teach replacing bases 241-528 of SEQ ID NO: 1 with a Neo cassette as now claimed.

Belo taught a transgenic mouse comprising a heterozygous or homozygous disruption the in the cerberus gene. Stanley produced the transgenic mouse by introducing a targeting construct that replaced most of exon I and all of exon II with an IRES-lacZ-Neo cassette into a mouse ES cell, transferring the ES cell into a mouse blastocyst to create a transgenic embryo, and implanting the blastocyst into a recipient female, wherein the embryo was allowed to develop to term (pg 268, col. 2 "Generation of Chimeric Mice"). Exon I and all of exon II replaced by Belo "correspond to" nucleotides 241-528 of SEQ ID NO: 1 as claimed because they overlap. The mice taught by Belo inherently have "anti-depressive behavior" (17) and "decreased average velocity and decreased total distance traveled" (26) and decreased time immobile in a tail suspension test (28) and increased number of fecal boli during an open field test (29) as claimed because the mice of Belo have the same disruption as the mice

described by applicants. Without evidence to the contrary, the mouse Cer1 gene disrupted by Belo inherently encodes SEQ ID NO: 1.

The declaration by Michael Leviten filed 11-22-05 attempting to swear behind the date of April 2000 (Stanley) is moot in view of the effective filing date of the claims as newly amended.

Claim Rejections - 35 USC § 103

Claims 8 and 18 remain rejected and claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conquet (Neuropharm. 1995, Vol.34, No. 8, pg 865-870) in view of Mara (GenBank Accession No: AA120122, Nov. 21, 1996) for reasons of record.

Conquet made a mouse with a heterozygous and homozygous disruption in a gene by inserting LacZ and neo genes into the gene (¶ bridging pg 865-866; pg 886, Fig. 1A; pg 868, Fig. 3 and col. 1, line 6-8 and 17-20). Conquet did not disrupt SEQ ID NO: 1.

However, Marra taught SEQ ID NO: 1.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to disrupt a gene in a mouse as taught by Conquet, wherein the gene was SEQ ID NO: 1 as taught by Marra. One of ordinary skill in the art at the time the invention was made would have been motivated to specifically disrupt SEQ ID NO: 1 instead of the glutamate receptor gene described by Conquet to gain clues to the function of SEQ ID NO: 1 in vivo. One of ordinary skill would have had a reasonable

expectation of successfully making a mouse based on the combined references because GenBank Accession No. AA914066 provided a coding sequence (mRNA or cDNA) that could easily be used to make homology arms capable of recombining with the Cerberus gene. While Conquet had knowledge of the genomic sequence, the genomic sequence was not essential to making the targeting construct used to make the mouse. Applicants' disclosure provides no description of how to use mRNA to make a knockout construct greater than the combined teachings of Conquet and Marra.

The nucleotides replaced by Conquet "correspond to bases 241-528 of SEQ ID NO: 1" because they are all nucleotides. Thus, the nucleotides of the cDNA of Marra replaced would also "correspond to bases 241-528 of SEQ ID NO: 1" as claimed.

Claim 17, 26-30 are not included in the obviousness rejection because those of skill would not have expected the Cer1 knockout mice to have anti-depressive behavior, decreased average velocity or total distance traveled in an open field test, decreased total time spent immobile in a tail suspension test, or increased numbers of fecal boli during an open filed test.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

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